REMARKS

The Rejection under 35 U.S.C. §103

The rejection of claims 1-15 under 35 U.S.C. §103, as being obvious over WO 02/45703 (WO 02) and WO 00/75114 (WO 00) is respectfully traversed.

In the Final Office Action, the evidence submitted on August 11, 2006, in the Declaration of Dr. Pieper regarding a showing of an unexpected synergistic advantage of the invention was not found convincing because a statistical analysis (i.e., standard deviation) of the results was not presented and there were undescribed columns of numbers in the data. Applicants respectfully point out that the undescribed columns of numbers standard were, in fact, the alleged lacking standard deviation (SEM) figures. Thus, a new corrected declaration of Dr. Pieper is filed herewith which adds the "SEM" descriptive for those columns of data in Annex 2. It was also noted that the table in Annex 2 contained another obvious error in that the Time was indicated to be in units of minutes, although it was believed to be clear that hours was intended. This correction is also made in the new declaration.

In view of the corrected declaration, applicants re-iterate their position that the data show unexpected results for the claimed invention and clearly and convincingly prove nonobviousness of the claimed invention. The basis for the rejection is that WO 02 teaches the compound of applicants' formula 2' for treating obstructive or inflammatory airway disease and WO 00 teaches a genus which broadly encompasses formula 2' and further generically suggests an option of co-therapeutic agents, including, among others, tiotropium bromide, for treating obstructive or inflammatory airway disease. Thus, the conclusion is made that there was a suggestion to combine applicants formula 2' compound with tiotropium bromide. This conclusion appears to be based on the assessment that two compounds taught for the same use would be expected to provide an additive effect for that same use.

The Declaration of Dr. Pieper proves nonobviousness because it shows that, unexpectedly, the combination of applicants' formula 2' compound and a tiotropium salt provides an effect that is significantly greater than an additive effect, i.e., a significant synergistic effect. This synergistic

effect was discovered by applicants and disclosed in the original application; see, e.g., page 2, lines 19-22. This advantageous effect could not have been expected from the prior art teachings.

Referring to Annex 2 of the declaration, the data show that the bronchoprotection activity from the combined treatment with formula 2' and tiotropium bromide is higher than the additive effect of the two compounds alone. Particularly, the bronchoprotection effect of the combination shows a lasting effect because a high amount of synergism is demonstrated hours after administration. At 6 hours post-administration the bronchoprotection effect of the combination (column D) is significantly higher than the calculated additive effect of the individual components. At 12 hours it is nearly twice as high as the calculated additive effect. And at 24 hours it is three times as high as the calculated additive effect. It is believed to be evident that the data demonstrate a highly significant synergistic effect of applicants' claimed combination.

The references provide generic teachings which, if the proper selections were made, could arrive at applicants' combination. However, the references provide no teachings that the particular combination of the formula 2' compound and a tiotropium salt is particularly preferred over the other combinations encompassed by the combined reference suggestions. Certainly, neither of the references provide any suggestion that this particular combination would provide a highly significant synergistic bronchoprotective activity.

For all of the above reasons, it is urged that the data clearly and convincingly establish the nonobviousness of the claimed invention over the cited prior art. Thus, the rejection under 35 U.S.C. §103 should be withdrawn.

For clarity of the record, applicants refer to the allegation in the initial Office Action that WO 02 teaches the use of the formula 2' compound together with corticosteroids and that the tiotropium compound 1 used in applicants' invention is in the same family as corticosteroids. This, in fact, is not correct. Tiotropium is not a corticosteroid nor in the same family as corticosteroids. This is known in the art and believed to be made clear in the WO 00 reference (page 17 first paragraph). Here, WO 00 refers to two classes of compounds useful as co-therapeutics. One class is anti-inflammatory agents and these include steroids, such as corticosteroids. A different class is bronchodilatory drugs and these include tiotropium. The art of record, therefore, shows that tiotropium and corticosteroids are in different classes and have different effects. Thus, is cannot be

said that corticosteroids and tiotropium are in the same family. Accordingly, WO 02 alone does not provide any suggestion to combine a tiotropium salt with its compound of formula I. In this light, it is submitted that the teachings of the art are not as close to the claimed invention as originally alleged and, thus, the burden of the showing of nonobviousness is not as high as may have been previously considered. In any event, the showing of nonobviousness is believed to be clear and convincing for the reasons stated above.

It is submitted that the application is in condition for allowance. But the Examiner is kindly invited to contact the undersigned to discuss any unresolved matters.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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